

Comments of Michael J. Thun, M.D. (on behalf of the American Cancer Society, Atlanta, GA)***Comment 1:***

The California Environmental Protection Agency (Cal/EPA) is to be commended for its comprehensive review of the scientific literature on Environmental Tobacco Smoke (ETS) as a Toxic Air Contaminant (1). This update of a previous Cal/EPA monograph (2) adds valuable information on the extensive clinical and experimental evidence regarding ETS and heart disease from studies published since 1997. It is notable that the previous Cal/EPA report was the first to draw widespread attention to the adverse cardiovascular effects of ETS exposure. This relationship is now well established, due in part to the groundbreaking contributions of Cal/EPA.

Response:

Thank you for these supportive comments, and for the thorough review and analysis of the document, in particular our evaluation of studies on the association between breast cancer and exposure to ETS. OEHHA staff was gratified to see the positive reception that the 1997 document received, and hope that the present update will prove similarly useful in promoting public health and scientific understanding of the effects of ETS.

Comment 2:

The current draft report concludes that ETS exposure is causally related to cancers of the lung, breast, and nasal sinuses (Page 7-1). The relationship between ETS and breast cancer is said to appear stronger for pre- than post-menopausal breast cancer. In this report, Cal/EPA again distinguishes itself by providing an update of the evidence on ETS and lung cancer, and by drawing attention to the accumulating evidence concerning breast cancer and second hand smoke. However, the conclusions of this report with respect to breast cancer conflict with that of a working group of the International Agency for Research on Cancer (IARC) (3). IARC characterized the evidence regarding ETS and breast cancer as "inconsistent". The conclusions of Cal/EPA and IARC also differ with respect to cancers of the nasal cavity and paranasal sinuses. Both the current and previous Cal/EPA report include cancer of the nasal cavity as causally related to ETS. IARC lists cancers of the nasal cavity and paranasal sinuses among the 15 cancer sites caused by active smoking, but does not designate either of these cancers as causally related to ETS.

Response:

There are a number of reasons why the conclusions of the Cal/EPA report may differ from other evaluations, such as that recently published by IARC. In the case of the association with breast cancer, we were able to include some studies and meta-analyses that were unavailable to IARC

at the time of their report. OEHHA staff and consultants also undertook different (and more extensive) analyses of data and metadata than those used by IARC. Even where the data considered are the same, different experts may reasonably come to differing conclusions. Details of the Cal/EPA report's conclusions in relation to breast cancer are discussed in subsequent responses. The conclusion in relation to cancer of the paranasal sinuses is also clarified in response to specific comments by Dr. Thun.

Comment 3:

The question of whether ETS, or more generally tobacco smoke, causes breast cancer is extremely important. If passive smoking does cause breast cancer, then policies that reduce ETS exposure will help to prevent this cancer and will strengthen the social mandate to protect non-smokers from second-hand smoke. However, if the evidence is not conclusive at this time, then a premature decision about causality could jeopardize the credibility of the entire review process. The current evidence that ETS exposure causes lung cancer and heart disease is convincing. It is crucial that other conditions be added to this list only if the evidence supporting a causal relationship can withstand careful scientific scrutiny.

Epidemiologists at the American Cancer Society (ACS) (Thun, Henley, Oltmanns, and Calle) have carefully reviewed the sections of the report pertaining to breast and nasal sinus cancers. We evaluated this evidence in relation to the Cal/EPA criterion that "chance, bias, and confounding can be ruled out with reasonable confidence" (page 1-9). At present, we do not believe that the published evidence meets these criteria for cancers of the breast or nasal sinuses, although we do believe that breast cancer in particular is an important topic for continuing research. We offer the following comments for consideration.

Response:

We thank Dr. Thun for his critical comments on our evaluation of the association between breast cancer and ETS exposure, and our conclusion of a causal association based on both epidemiological evidence and supportive data from the animal toxicology literature on specific constituents of tobacco smoke. We agree that the conclusion in relation to breast cancer and smoking is extremely important. We consider that the "credibility of the review process" is equally jeopardized by a premature decision in favor of causality, and by a failure to respond to new and important findings and analyses, which support that conclusion. We have received a number of comments about this conclusion, some supportive and some not. Having carefully reviewed the thoughtful comments by Dr. Thun and others (see below, and in other sections of the responses to comments) we stand by the conclusion expressed in the draft report, that the

existing evidence suggests that the association between ETS exposure and increased incidence of breast cancer may reasonably be considered causal. As an agency charged with a responsibility for the health of Californians, it would be equally detrimental (perhaps far more detrimental in terms of public health) to fail to inform the public of a risk where the evidence of an effect is credible and meets our criteria for causality.

General Comments

Comment 4:

- 1) The summary of the epidemiologic evidence concerning breast cancer (pages 7132 to 7-147) offers four hypotheses, listed below, to explain why published studies of active smoking and/or ETS exposure have not consistently found increased risk of breast cancer risk in exposed women. However, the discussion of this evidence, in terms of its consistency, strength and specificity, and limitations, is relatively brief. This section needs to be expanded and broadened to assess systematically the extent to which published studies support or conflict with the hypotheses proposed. It also needs to consider other potential limitations of case control studies, particularly biases that may be introduced by the use of highly selected reference groups.

Response:

The hypotheses that have been put forward by various authors and briefly presented in the review are considered to be just that, hypotheses. These indeed are supported by findings in various studies and as Dr. Thun mentions below are biologically plausible. We have not attempted to prove these or quantify the level of supporting evidence, as that is beyond the scope of our work. Since they are considered hypotheses their disproof would not be evidence that the data found in the epidemiologic studies in question are wrong, but merely that there is a different reason for the results. However, we do provide further analysis of these questions in these responses to comments, and in the revised version of the final document, insofar as they are helpful in developing and testing our conclusions with regard to the associations between exposures to tobacco smoke and breast cancer.

In the final sentence, the identification of highly selected reference groups as a potential source of bias is taken as referring to the fact that the referent exposure category “never exposed to ETS” constitutes a relatively small subgroup (as Dr. Thun notes later, 10% of non-smokers in Johnson 2000) of the total sample of non-smoking women. It is inappropriate to describe the

identification of these referent individuals as “selection” in the sense usually employed since they represent all members of the sample population having the specified data value. Any underlying differences in their characteristics relative to the study sample as a whole would arise not from selection bias but from the existence of other exposures or characteristics that are highly correlated with the status of non-smoker not exposed to ETS, which also influence disease outcome. The most likely factor to fit in that category would be alcohol, which has been controlled for as an independent variable in most of the studies in question. Neither Dr Thun’s comments nor OEHHA’s review have identified other major confounding variables which have been consistently ignored in the study designs. The alternative to use of this referent group would be to knowingly misclassify some percentage of the 90% (Johnson, 2000) of non-smokers who are exposed to ETS as nonexposed. In studies where only 10% of subjects are exposed to a factor (for example occupational studies), researchers do not doubt results because this is “highly selected group” but rather control for known risk factors and report the results they observe. It seems curious to worry about refining the control group to mean not-ETS exposed as som how different.

Comment 5:

- 2) The hypotheses proposed to explain the lack of association between breast cancer and active and/or passive smoking can be paraphrased as follows (page 7-133):

Response:

OEHHA thanks Dr. Thun for his thoughtful analysis of this issue. However, the paraphrase presented in the following comments does to some degree mischaracterize the hypothesis that OEHHA chose to evaluate. Individual responses given below will attempt to address this, and it is hoped that the fuller description inserted into the revised document will remedy this evident lack of clarity for future readers. OEHHA has also taken the opportunity in revising the document to include references to some additional papers that have appeared in the scientific literature after the preparation of the public review draft (and, in some cases, after the comments received were written).

Comment 6:

- a. The dose-response relationship between exposure to tobacco smoke and breast cancer risk may be non-linear. According to this theory, low doses of tobacco smoke (such as result from ETS exposure), may increase risk, whereas higher doses (such as those due to active smoking) may obscure this risk, because of the anti-estrogenic effects of active smoking. This theory is proposed to explain why ETS may increase breast cancer risk, even though active smoking does not.

Response:

OEHHA prefers to characterize the non-linearity of the dose-response for breast cancer to tobacco smoke as an observation rather than a theory. As detailed in the document, and elsewhere in these comments, several independent studies have shown that, when a genuinely non-exposed referent group is used, subjects with exposure to environmental tobacco smoke have an increased risk of breast cancer which is in fact similar to the risk faced by moderate active smokers. One theory which has been advanced to explain this observation is that the higher doses of tobacco smoke experienced by active smokers have an anti-estrogenic effect which may, at least for some women, be sufficient to reduce the risk of (estrogen dependent) breast cancer to a level similar to, or even below, that experienced by those with passive exposure only. It should be apparent that OEHHA is not arguing that active smoking does not increase breast cancer risk. In order to explain the essentially null results of Wartenberg et al., and other large prospective studies where tobacco exposure in the referent group was inadequately determined, it is necessary only that the risk for active smokers be reduced to approximately that experienced by passive smokers (which is, according to other studies, perhaps 1.5 – 2 times higher than that for unexposed women), not to zero.

Comment 7:

- b. Tobacco smoke may increase breast cancer risk only in a genetically susceptible subgroup of women. This theory suggests that studies that combine all women and do not stratify on genetic susceptibility may obscure an association.

Response:

There are a number of studies that suggest that this may be an important consideration. It should be noted that there is likely not one single genetically susceptible subgroup, but a wide

range of such groups depending on the polymorphism of several genes, which are hypothesized to be important in the metabolism of various tobacco-related carcinogens. Also, the relationship is further complicated by the fact that interactions between metabolic status, level of exposure, age at exposure, and estrogen levels may occur, such that some subgroups may only show differential responses at certain (e.g. lower) doses (Vineis et al., 1994) or depending on pre- or post-menopausal status. These complexities, may account for the different results seen in such studies, which should be characterized as diverse rather than conflicting.

Comment 8:

- c. Human breast tissue may be vulnerable to exposure to tobacco smoke only during certain critical time periods. For example, vulnerability may be greatest between menarche and first pregnancy, as is the case with ionizing radiation. Epidemiologic studies that define ETS exposure in other ways (such as years of childhood exposure, cumulative exposure, or continuing exposure) may misclassify the biologically relevant exposure and thus fail to detect a real association.
- d. Tobacco smoke may affect certain types of breast cancer but not others. For example, some studies have reported increased risk only in relation to premenopausal breast cancer.

Response:

The document lists a number of studies where age-related differences in sensitivity to tobacco smoke appear to produce differences in response to either active or passive smoke exposures. OEHHA has noted these observations and attempted to incorporate them into the overall explanatory hypothesis, as the commenter notes. Related to this point is that prospective cohort studies, in addition to having difficulty ascertaining exposure over a long time period by asking questions in the beginning of the study about largely spousal exposure to ETS, do not ascertain childhood exposures well if at all. The subjects need to remember back to childhood to provide responses about childhood exposure (which were not even asked in most of the cohort studies. Thus, peri-pubertal exposures are poorly ascertained. Most peri-pubertal exposures are largely to ETS and not mainstream smoke. The different chemical constituents (higher PAH and carcinogenic amines in sidestream than mainstream smoke) results in different exposures peripubertal relative to older children and adults. This too complicates the picture and may be

another reason that it is difficult for prospective cohort studies to find an effect of ETS on breast cancer.

OEHHA does not argue, as implied in point 2d, that tobacco smoke affects only certain types of breast cancer but not others, nor was it suggested that there is a systematic difference between pre-menopausal and post-menopausal cancers. (OEHHA is aware that cancers diagnosed after menopause on average show a lesser degree of estrogen dependence, but surely this reflects selection during the progression phase rather than any necessary differences in the initial causation, which in either case probably occurred many years previously.) In summary, OEHHA is assuming a difference in sensitivity with age and developmental status of the breast [as delineated for instance by Lash and Aschengrau (1999)] – i.e. differences in the breast rather than the cancer caused. Differences between cancers may or may not exist, but this is not a part of the hypothesis under discussion.

Comment 9:

- 3) Any or all of the above hypotheses are biologically plausible. However, the hypotheses themselves do not constitute evidence that active or passive smoking causes breast cancer. Additional evidence supporting these hypotheses is particularly necessary because of the large published literature that shows no overall relationship between active smoking and breast cancer. As noted by IARC; "the lack of an association with active smoking weighs heavily against the possibility that involuntary smoking increases the risk of breast cancer, as no data are available to establish that different mechanisms of action are in play at the dose levels of active and involuntary smoking." In revising the report, Cal/EPA should systematically examine which studies (basic, epidemiologic and other) support each hypothesis and which do not. The following points, in particular, need attention.

Response:

As detailed below, and in the revised document, OEHHA disagrees with the assertion in this comment, and in the IARC review, that there is no association between active smoking and breast cancer. The failure of several large studies to reveal such an effect reflects those studies use of referent groups whose lifetime exposure to ETS is uncharacterized, and probably significant. In view of the data suggesting age-dependence of sensitivity, and in particular a higher sensitivity of breast tissue to carcinogenesis during adolescence and prior to the first pregnancy, the use of spousal smoking habit as a sole, dichotomous measure of ETS exposure seems egregiously inadequate since it largely fails to capture the extent of exposure during the

*period of greatest sensitivity. The expectation of a strong link between breast cancer and ETS exposure and a correspondingly stronger association with active smoking is valid only if it is assumed that the dose response relationship for tobacco smoke of any type is linear and that mainstream smoke and ETS are equivalent chemically. Although epidemiological studies frequently assume such a dose-response relationship (typically, *faute de mieux*), in this case this assumption is neither necessary, nor supported by the data.*

OEHHA has proposed that a) the observed association between ETS exposure and breast cancer is real and causal and b) that the dose-response for the mammary carcinogenic effect of tobacco smoke is non-linear, especially toward the higher dose ranges associated with active smoking. OEHHA sees this as primarily a data-based hypothesis which succeeds in unifying to a substantial degree all of the observed epidemiological results, without having to resort to any extraordinary deconstruction of the relevant studies. The converse hypothesis, that there is no such carcinogenic effect of tobacco smoke at any dose level, requires detailed, and individually different, dismissals of a substantial number of studies by assuming unproven statistical imbalances, unidentified confounders, and failure of recognized methods for dealing with confounding and covariance. The existence of a mammary carcinogenic effect of tobacco smoke is supported by numerous studies of its individual components, which include several IARC-recognized human carcinogens. Additionally, there are several explanatory hypotheses which can be advanced, with varying degrees of experimental and epidemiological support, for the non-linear dose response relationship. The existence of such plausible mechanistic hypotheses certainly provides support for OEHHA's analysis, but it is not necessary that any or all of these mechanistic hypotheses be proven beyond doubt; the key assumption of causality and non-linear dose response precedes the explanatory hypotheses rather than being derived from them.

Comment 10:

- a. The report should acknowledge that extensive epidemiologic data shows no overall association between active cigarette smoking and incident breast cancer, in analysis that include women exposed to ETS in the referent group. A meta-analysis of 53 epidemiological studies found that, among 22,255 women and 40,832 controls who drank no alcohol, there was no overall association between active cigarette smoking and breast cancer [RR=0.99 (95% CI=0.92-1.05)] (Figures 1 & 2) (4). All of the studies in this analysis had individual information on reproductive risk factors for breast cancer and hormonal therapies with which to control for these factors. Alcohol consumption was

unequivocally associated with breast cancer in these studies and correlates strongly with active smoking (and possibly with ETS exposure). Therefore, it is essential that studies of active or passive smoking in relation to breast cancer be able to control for alcohol consumption, which some have not.

Response:

The above mentioned meta-analysis makes no claims of considering in any way passive smoke exposure. Under the methods section they state that “no attention was given to the reported associations of breast cancer with environmental tobacco smoke exposure”. If, as we believe to be true, the data supports a relative risk of ETS that is in a range that approximates that of active smoking (for whatever reason) and if most non-smokers have had significant ETS exposure which is certainly the case, particularly in the many older studies included here, then it is not surprising that this analysis would be unable to identify a risk. In effect, the analysis is to a large degree comparing exposed with exposed.

Reynolds et al. (2004) in their recent prospective study, which at your suggestion we have added to the report, did find a significant association between active smoking and breast cancer that increased with increasing duration and intensity of smoking. When the analysis was limited to the 35,123 nondrinkers in this cohort, current smokers continued to have a significantly elevated risk of breast cancer (HR 1.66, 95% C.I. 1.15-2.40). This is in fact a higher HR than the study as a whole and refutes concerns that associations between smoke exposure and breast cancer are actually measuring a surrogate of alcohol exposure.

An interesting paper by Zhang et al. (2004) has been published as an abstract since the initial draft of our document and will be included in the discussion. In that cohort study of 49,165 Canadian women aged 40 – 59 were followed for 14 years: Women had an elevated risk of breast cancer death if they had smoked 30 years or more (HR = 1.90; 95% CI, 1.29, 2.80), compared to never smokers. When compared to nondrinkers who had never smoked, light to moderate drinkers (>0 and <20 g/day of alcohol) who smoked for more than 30 years were twice as likely to die of breast cancer (HR = 1.98; 95% CI, 1.13, 3.48). Heavy drinkers (20+ g/day of alcohol) who smoked this long had almost a three-fold risk of breast cancer death (HR = 2.72; 95% CI, 1.30, 5.67). Heavy drinkers who smoked 40+ cigarettes/day experienced an almost four-fold risk of breast cancer death (HR = 3.85; 95% CI, 1.34, 11.09). There was a

positive dose response relationship between years smoked and breast cancer mortality ($p < 0.05$) among both drinkers and non-drinkers, after adjusting for cigarettes per day smoked, alcohol consumption, and other potential confounders. Apparent in this study is an at least additive effect of alcohol and smoking and an effect of smoking independent from drinking. We agree with the commentator's suggestion that it is very important to control for alcohol consumption and have weighed our consideration of studies accordingly. Though not always clearly identified in the individual papers as such, many of the recent studies do include control for alcohol consumption. We have made additional notations in the OEHHA document to clarify where papers have considered alcohol consumption in the revised document.

Zhang B, Ferrence R, Cohen J, Ashley MJ, Bondy S, Rehm J, Jain M, Miller A, Rohan T (2004) published as an abstract in the abstracts of the 37th annual meeting of the Society for Epidemiologic Research (June, 2004). <http://www.epiresearch.org/meeting/abstractbook.pdf>

Comment 11:

- b. At least six studies of active smoking and breast cancer have examined the association with and without exclusion of ETS exposed women from the referent group (Figure 3). Four of these studies show some increase in the relative risk (RR) estimate when ETS women are excluded (Morabia 1996, Johnson 2000, Kropp 2002, Egan 2002) while two show either no increase (Marcus 2000) or a decrease (Reynolds 2004). In no study is the effect of this exclusion statistically significant. The increase in the relative risk estimate resulting from the exclusion appears to be larger and more consistent in the case control studies than in cohort analyses, raising concerns about potentially biased reporting of exposure in retrospective studies. At least five case control studies featured in the Cal/EPA report (Sandler 1985, Morabia 1996, Lash 1999, Johnson 2000, Kropp 2002) and one prospective study (Reynolds 2004) found an association between active smoking and breast cancer incidence, even when they did not exclude ETS exposed women in the referent group. The observed association is so strong in two studies (Sandler 1985 & Morabia 1996), that if it were real, some increase in risk would be apparent in most studies of active smoking, irrespective of methodological differences. Cal/EPA needs to address the potential for biased reporting of exposure in case-control studies in the section on "Limitations of studies (7-139 to 7-140), and possibly in the summary on page 7-147.

Response:

Thank you for providing the attached figures. Figure three is, however, somewhat confusing to us. It is labeled as "breast cancer among current active smokers..." though in Johnson the data for this analysis of the effect of inclusion or exclusion of passive smokers in the referent is given

for “ever smokers”. In Morabia (1996) the data is also for “ever smokers” and is given for three levels of exposure that cannot be combined without the raw data. Using only one level’s data will give a wide confidence interval, as the selected population will be relatively small. While Kropp’s data is for current smokers, it would clearly be more appropriate, and provide tighter confidence limits, if current and former smokers were combined for an index similar to the other studies “ever smoker” category. In a qualitative way, we believe that this figure does make a point that a lifetime exposure history is important to consider. The four case-control studies that show an increase in ORs are studies with measures that include different life-stages as well as assessment of home, occupational and other exposures. The two cohort studies that do not find a difference (or even a slight decrease) are ones in which important measures were not collected.

Although Figure 3 provides a nice graphical representation of the effect of removing subjects with passive smoke exposure from the control groups, it cannot be used to make a statement about the “statistical significance” of the effect of the exclusion. Excluding subjects with passive smoke exposure sharply reduced the sample size in most of the analyses presented. This has the effect of increasing the standard error of those estimates and increasing the size of the confidence intervals. This makes the difference harder to detect. However, overlapping confidence intervals do not imply that two odds ratios are not statistically different. A general rule of thumb states that “confidence intervals associated with statistics can overlap as much as 29% and the statistics can still be significantly different” (van Belle G., 2002, Statistical Rules of Thumb. New York: John Wiley). This is true because the standard error of the difference between two statistics is smaller than the sum of the individual standard errors. Therefore, the odds ratios from the Johnson et al. (2000) study may actually be statistically different, since a reduction of the confidence intervals by 29% would cause them to not overlap. Many authors perform “sensitivity” analyses with their data to see whether their results are robust to changes in definitions of disease, definitions of exposure, and restriction to subgroups of subjects. In many cases, these analyses have reduced power. However, they are used as a qualitative measure of robustness, and authors do not make statistical comparisons between estimates obtained from the sensitivity analyses. Therefore, Figure 3 should be used as a qualitative illustration of the effect of removing passive smoke exposure from the control groups.

Exposure reporting bias in case-control studies comes either from interviewer bias (where study staff interviewing subjects probe more deeply with cases -- not an issue if data were obtained by questionnaire with no interviewer) or recall bias (where cases try harder to remember past exposure than controls.) With these issues, the concept of “blinding” of the interviewers and subjects to the hypothesis of the study is important. If the cigarette smoke hypothesis was the main purpose of the study, and the interviewers and/or subjects were aware of the hypothesis, then bias might have occurred. At the other extreme, if the smoking hypothesis was not the main purpose of the study and active/ETS smoking was among a long list of questions, it is unlikely that bias would have occurred. In response to this comment we have reviewed each case control study individually for potential for bias and included this review in the “Limitations of Studies” section of the breast cancer summary. It is the opinion of OEHHA that the majority of the studies considered adequately addressed potential for bias and studies that did were given more weight in our review. Below are examples of case-control studies consideration of bias.

Sandler et al. (1985). Mailed questionnaires – no interviewer bias. However, the focus of the study appeared to be smoking. Interview of 649 relatives of subjects showed good agreement between subjects’ and relatives’ responses regardless of case/control status, suggesting minimal recall bias. Also, hypothesis that parental smoking may cause cancer was not widely known at the time.

Smith et al. (1994). The data for this study derived from the UK National Case-Control Study Group that was designed to investigate the relationship between contraceptive use and breast cancer. Data were also collected on other lifestyle factors such as smoking by interview. However, information on passive smoke exposure was obtained via a self-completed questionnaire returned by mail, thus minimizing interviewer bias but the possibility of recall bias remained.

Morabia et al. (1996). Data collected from cases and controls under the same conditions by trained interviewers who were not involved in the recruitment and who were blinded to the case/control status. Questions covered the major known or postulated risk factors for BC. Interview was approximately 45 min. of which 20 min were devoted to smoking history. Selection bias was addressed by collecting smoking status on non-participants and indicated

there was some “slightly conservative selection bias (that) may be due to a small number of current smokers among nonparticipating controls being reluctant to tell their true smoking status.” Questions relating to the subject’s attitude regarding passive smoke and smoking in general were compared to their reported exposures. It was postulated that, for similar levels of exposure, if cases were more likely to report having been passively exposed, they would be more likely to report being more preoccupied by passive smoke in their everyday lives than were controls. The data did not support this so the authors suggest recall bias was minimal. As with Lash and Aschengrau, the authors suggest that passive smoking is not associated with breast cancer in the public’s mind, thus minimizing disease-dependent recall bias. They calculated that if due to erroneous recall, 15% of the unexposed cases and 0% of the unexposed controls had been misclassified as passive smokers, the unbiased crude OR for ever-passive smoking would still be significant (1.8, 1.2;2.8). The Morabia study did suggest increased risk beyond what you would expect for active smokers compared to never smokers. This may indicate that the sampling had an excess of smoking cases or a deficit of smoking controls, and that passive and active risks may be higher than one would expect for passive smoking and passive-controlled active smoking (as was the case compared to the other ETS-breast cancer studies), but not that there would be no risk.

Millikan et al. (1998). This study was also based on the CBCS (see Marcus) and so used interviews by trained nurses. Little information was presented to assess possible bias. They did note that smoking prevalence among controls was 20%, similar to a recent survey conducted among women in North Carolina. Thus a positive association between smoking and BC is not due to high refusal rates (for interviews or blood draw) among controls who were smokers.

Lash & Aschengrau (1999). Structured interviews by trained interviewers covered information on demographics, reproductive events, smoking and medical conditions. This was a retrospective study so some recall bias could have occurred. “However, the substantial associations that were found were within the strata defined by time periods calculated from a series of responses. We do not expect these derived exposures to be susceptible to recall bias.” Without knowing more about the study design, it’s hard to say if this is true. “ Further, neither active nor passive exposure to cigarette smoke has been closely related to breast cancer risk, so recall of exposure should not depend on disease status. However, the widely held perception

that smoking causes cancer may contribute to some disease-dependent recall of exposure to tobacco smoke.”

Johnson et al. (2000). Questionnaires were mailed, thereby eliminating interviewer bias. ETS questions were among many others on breast cancer (BC) risk factors. Data from subjects with one of 18 other cancers, including a large sample of lung cancer cases, were also collected in the same data collection (the National Enhanced Cancer Surveillance System). Possible recall or response bias was examined by comparing 71 never smoking women with lung cancer and 714 never smoking women controls, the same pool of controls used for the breast cancer analysis. They found an age-adjusted OR of 1.2 (0.7; 7.1) for the association between lung cancer and years of home ETS. More recent meta-analysis found an unadjusted risk of 1.2 (1.1; 1.4) for lung cancer among lifelong nonsmokers living with a smoking spouse. The authors use the lung cancer results to suggest that bias is likely not seriously affecting the BC risk estimate. Furthermore when Johnson et al. examined the risk of active smoking in the traditional way (ignoring ETS exposure) the observed risk was 1.0 for premenopausal breast cancer and 1.2 for postmenopausal breast cancer, consistent with the literature.

Delfino et al. (2000). Data were collected by interview of women scheduled to receive breast biopsy to rule out mammary carcinoma. Prior to biopsy, women took a self-administered questionnaire on risk factors. The study included only subjects whose questionnaires were returned by mail prior to receiving diagnosis. Eligible patients, participants and interviewers were all blind to case/control status. Interviewer and reporting bias were thus minimized. Participation rates were similar between those with and those without a diagnosis of cancer.

Morabia et al. (2000). This was a population-based study presented to participants as an on-going survey of women's health, the aim of which was not specified. Trained interviewers were blind to case/control status. Interviewer and reporting bias appear to have been minimized in this study, but recall bias was not specifically addressed. However, this study appears to be based on the same group as Morabia et al (1996), so presumably the same bias controls apply.

Marcus et al. (2000). This was a population-based study (Carolina Breast Cancer Study, CBCS). Interviews included administration of standardized questionnaire that covered established and suspected risk factors. Interviewer bias can't be ruled out. Authors report that

response rate varied by age and race, however, stratification by age and race subgroups gave ORs similar to main group. They suggest that differential recall between cases and controls regarding adolescent smoke exposure was unlikely since an association between adolescent smoke exposure and BC is not generally perceived. On the other hand, the authors acknowledge that misclassification is likely regarding the timing of thelarche vis-à-vis smoke exposure but they suspect it would be non-differential.

Krajinovic et al. (2001). Data were collected by interview in an earlier breast cancer study. Smoke exposure was one of several risk factors characterized as part of a study of gene-environment interactions. Without a more complete description of the original study, it's difficult to assess the potential biases at work in this study.

Kropp et al. (2002) used self-administered initial questionnaires (so no interviewer bias at this stage) on BC risk factors among which were five questions on active smoking. There was a computer-assisted follow-up telephone interview by interviewers blinded to the subjects' case/control status. There was "no great change in recall for active smoking between the first questionnaire and the follow-up interview even though smoking was only a minor aspect of the initial questionnaire. Taking into account the good quality of the other assessed factors, it seems unlikely that the reporting of active or passive smoking should be greatly biased by case/control status."

Band et al. (2002). Mailed questionnaires investigated occupational risk factors of which smoking history was a small part, so no interviewer bias was involved. The study was population-based with a high response rate thus minimizing selection bias. In addition, the proportion of never- and ever-smokers was similar among responders and non-responders for both cases and controls. However, the information for non-responders was obtained for only small subsets. The authors claim that recall and misclassification of age at commencement of smoking was not likely to systematically differ between cases and controls since smoking was not generally perceived as related to breast cancer. The absence of information on passive smoking could have led to misclassification of passive smokers as non-exposed but this would bias towards the null.

Lash & Aschengrau (2002). Data were collected by trained interviewers on demographics, smoking history and other risk factors. The only information in the paper regarding potential bias is: “Given that smoking history and history of residential passive smoke exposure should be well recalled, and given that an earlier investigation using a similar survey and population yielded causal results, we doubt that non-differential misclassification of exposure status accounts for the null results reported here.”

Shrubsole et al. (2004). In this population-based case-control study, data on demographics, health, activity, diet, and ETS exposure were collected by trained interviewers. The use of structured questionnaires is the only study feature mentioned in the report that may have limited interviewer bias. While reports of lifetime ETS exposure excluded childhood exposure, recall bias is still a possibility. Assessment of workplace ETS exposure was limited to the preceding five years but assumed to reflect longer-term exposure. However, this assumption was not verified. Selection bias is thought to have been limited by the population-based design and the high participation rate (91.1%).

Comment 12:

- c. Perhaps the most critical factor not considered by the Cal/EPA report is the potential for bias in studies that exclude women with any exposure to passive smoking from the referent group. This is particularly problematic in case control studies where women recall their ETS exposure retrospectively, already knowing whether they have breast cancer. Most women in Western countries who are old enough to develop breast cancer have had substantial past exposure to ETS. The subgroup of women designated as never-active, never passive smokers comprises a small percentage of all never-smoking women (about 10% in the study by Johnson et al., 2000). Reliance on a small and highly selected referent group may introduce serious problems with both the validity and statistical precision of these studies. In general, the published studies do not provide information about the demographic and behavioral characteristics of women in the referent group who report neither active nor passive smoke exposure. Reliance on a highly selected control group may introduce more biases than it removes.

Response

In the final sentence, the identification of highly selected reference groups as a potential source of bias is taken as referring to the fact that the referent exposure category “never exposed to ETS” constitutes a relatively small subgroup (as Dr. Thun notes, 10% of non-smokers in Johnson 2000) of the total sample of non-smoking women. It is inappropriate to describe the

identification of these referent individuals as “selection” in the sense usually employed since they represent all members of the sample population having the specified data value. Any underlying differences in their characteristics relative to the study sample as a whole would arise not from selection bias but from the existence of other exposures or characteristics that are highly correlated with the status of non-smoker not exposed to ETS, which also influence disease outcome. The most likely factor to fit in that category would be alcohol, which has been controlled for as an independent variable in most of the studies in question. Neither Dr Thun’s comments nor OEHHA’s review have identified other major confounding variables which have been consistently ignored in the study designs. The alternative to use of this referent group would be to knowingly misclassify some percentage of the 90% (Johnson, 2000) of non-smokers who are exposed to ETS as nonexposed. In studies where only 10% of subjects are exposed to a factor (for example occupational studies), researchers do not doubt results because this is “highly selected group” but rather control for known risk factors and report the results they observe. It seems curious to worry about refining the control group to mean not-ETS exposed as some how different.

It is a feature of many epidemiologic studies that comparisons are made to groups representing relatively small minorities of the general population. In the study that Dr. Thun cites above as important (Hajima), those with no alcohol consumption are utilized as the referent and the paper draws the earlier cited conclusion that alcohol is directly associated with breast cancer (and not smoking). The demographic characteristics of those women in the combined 53 studies are not well defined.. They (particularly the heavy drinkers) might be considered a highly selected exposure group by these proposed standards. In the California Teachers prospective cohort (Horn-Ross P, et al. Cancer, Causes, and Control 2002) only women with 20 grams of alcohol intake/day or greater showed a significant increase in risk for breast cancer. At least in that California cohort those with 20 grams or more intake comprise only 8% of all women. In addition, in further analysis of the California Teacher’s cohort Reynolds et al. (2004) found that among never smokers, those with increasing alcohol consumption were much more likely to be exposed to ETS (5-15 gm/day OR for ETS exposure= 1.70: 95% C.I. 1.61-1.80). If as we propose, ETS is a causative factor in development of breast cancer, the increased exposure to ETS in drinkers may account for a portion of the observed association with alcohol. Any study that characterizes participants in quartiles or quintiles selects only 20 or 25% of the potential

population as a control group. The studies that utilize women non-smokers not exposed to ETS have been conducted in numerous countries throughout the world. Certainly in some Asian studies non ETS exposed is not a small minority of women non-smokers. We do not see any indication that there is likely some unmeasured factor related to the disease that is disproportionately present (and not already controlled for) in a non-ETS exposed control group that would preclude it's selection as a comparison population.

In the group of studies that look at ETS exposure and breast cancer there is a wide range of values for the percentage of referents who are “unexposed” to ETS due to the various methods of defining unexposed as well as characteristics of the populations studied. Only Johnson, Egan, and Smith have case or control percentages of unexposed below 20%. In the Johnson study, the pre-menopausal group had only 6% of the cases unexposed, and 15% of the controls. However, when they added those whose exposure was up to ten years to the referent group (in order to stabilize the estimates), the OR for more than 10 years of exposure became 2.0 (95% CI, 1.2-3.3), and with this expanded definition, case non-exposure became 17%, and control non-exposure 29%. Even with a less precise but larger referent, the OR is still high and even more statistically significant. Below is a chart of the percentages of non-exposed cases and controls in various studies that evaluate passive smoke exposure and breast cancer. Most of the studies that broke out those controls not exposed to ETS report a larger percentage of the control group as not exposed than the 10% figure from Johnson et al. 2000 cited in the comment.

<i>Study</i>	<i>Cases not exposed to ETS</i>	<i>Controls not exposed to ETS</i>
<i>Hirayama</i>	20%	24%
<i>Sandler</i>	41%	57%
<i>Smith</i>	5%	13%
<i>Morabia</i>	22%	39%
<i>Milikan</i>	36%	35%
<i>Lash 1999</i>	34%	33%
<i>Delfino</i>	52% (low risk pool)	73% (low risk)
<i>Zhao</i>	35%	56%
<i>Jee</i>	No data available (NDA)	NDA
<i>Johnson</i>	11%	17%
<i>Nishino</i>	70%	58%
<i>Kropp</i>	22%	32%
<i>Lash 2002</i>	26%	21%
<i>Egan</i>	9.8% (low risk)	NDA

Comment 13:

- d. In summarizing the epidemiological evidence (pages 7-132 to 7-139), Cal/EPA should acknowledge that three large prospective studies in the United States (Egan 2002, Wartenberg 2000, and Reynolds 2004 [published after the Cal/EPA report]) found no increase in breast cancer risk associated with ETS exposure. These studies controlled for the other established risk factors for breast cancer and collected information on tobacco smoke exposure before the diagnosis of breast cancer. In at least two of these populations (the ACS cohort and the Harvard Nurses' study) spousal exposure to ETS exposure has been associated with both lung cancer and heart disease. The prospective data should be considered far more seriously in weighing the totality of the evidence than has been the case in the current draft.

Response:

We have indicated more clearly that three large prospective studies in the United States (Egan 2002, Wartenberg 2000, and Reynolds 2004 [published after the Cal/EPA report]) found no increase in breast cancer risk associated with ETS exposure, that these studies controlled for the other established risk factors for breast cancer and collected information on tobacco smoke exposure before the diagnosis of breast cancer; and that in at least two of these populations (the ACS cohort and the Harvard Nurses' study) spousal exposure to ETS exposure has been associated with both lung cancer and heart disease. Although cohort studies in general have the potential to be preferable for examination of risk, all three of these studies suffer from seriously incomplete measures of passive smoking exposure. The ability to determine a risk associated with ETS exposure and lung cancer and cardiovascular disease in the ACS and Harvard Nurses Cohorts but not find a risk for breast cancer may result from various factors. Cardiovascular disease is very sensitive to more recent exposure (Whincup et al., 2004) and therefore less complete historical data may be less of an impediment than for breast cancer. Exposures during the critical period of susceptibility between onset of adolescence and delivery of first baby, a period of rapid proliferation and differentiation of breast cells of the lobules and ducts and a known period of increased sensitivity to carcinogenesis, are likely to be of special importance to the risk of development of breast cancer. These windows of susceptibility present a substantially different picture than for lung cancer for which the data indicate a very linear dose response. The data collected by these studies may more closely reflect the important exposure in the case of lung cancer than in the more complicated scenario of breast cancer. The potential impact of this serious shortcoming in exposure measurement is addressed by Rothman and Greenland (Modern Epidemiology, 2nd edition) and were addressed in the earlier draft for the first two studies and in the revised draft for the Reynolds paper. A fundamental requirement for study validity is a level of accuracy in exposure ascertainment. In regards to the prospective studies of ETS and breast cancer, they have not to date included studies that have considered all important measures of lifetime ETS exposure. In the literature on ETS and lung cancer, it is generally considered that the most influential study is that of Fontana et al., which is indeed a case-control study that represented the best exposure history in its design by including all relevant exposures, a large diverse population, and cotinine measurements for exposure assessment.

While it is true that, in the prospective studies exposure is ascertained prior to disease onset and that this is a desirable feature, exposure during the critical period of adolescence and young adulthood is obtained by retrospective history since enrollment is typically well beyond that time in life. In this case, the exposure history in case-control and prospective studies suffer from the same drawbacks. The problem of reporting bias related to retrospective studies is mitigated as the potential link of smoking or ETS to breast cancer is not commonly known to the public.

An example of the importance of adequate exposure history is found in a paper by Eisner et al. (2001). Many studies, including both prospective and case-control studies, utilize a form of yes/no questioning of spousal smoking habits to determine exposure. In other words, exposed is often determined by the question, “does your spouse smoke?” with no consideration of smoke exposure in childhood or in adult workplace or other settings. Eisner found that “Only a minority of subjects who lived with a smoker reported any domestic exposure during the previous 7 days (6 out of 17, 35%)”. In contrast to those findings, Eisner found that all subjects with workplace exposure reported recent exposure at work. Janson et al. (2001), provide an example of how results may be affected by the resulting misclassification. The authors note a non-significant elevation of risk of asthma for any workplace or home ETS exposure. Examined individually, workplace exposure was associated with a higher statistically significant risk and home exposure with no apparent risk. In this case, home exposure was defined as living with at least one smoker, whereas workplace exposure ascertained regular smoking in the room where they worked. These findings indicate that as a historical marker of exposure, questions regarding exposure to ETS at work may be more important than simple spousal smoking determination. In the Reynolds “teacher’s cohort”, they have noted that beginning in the 1980s workplace exposure had become the primary exposure source.

In the questionnaire for women in the American Cancer Society Cancer Prevention Study 2 upon which the Wartenberg cohort study was based, the question upon which exposure to environmental tobacco smoke was determined was as follows:

Whether or not you smoke, on the average, how many hours a day are you exposed to cigarette smoke of others: At home____ At work____ In other areas_____.

Depending on when in your life you are asked this question, the answer could vary widely and so therefore does the exposure assignment. This points out the importance of adequate exposure history in determining classification. Given this example, one can understand why one might see different results from studies that include fuller, lifetime exposure histories than from those studies that ascertain exposure only at a single point in time or a single exposure location.

Eisner MD, Katz PP, Yelin EH, Hammond SK, Blanc PD. Measurement of environmental tobacco smoke exposure among adults with asthma. *Environ Health Perspect.* 2001 Aug;109(8):809-14.

Janson C, Chinn S, Jarvis D, Zock JP, Toren K, Burney P (2001). Effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function, and total serum IgE in the European Community Respiratory Health Survey: a cross-sectional study. *Lancet* 358(9299):2103-9.

Whincup PH, Gilg JA, Emberson JR, Jarvis MJ, Feyerabend C, Bryant A, Walker M, Cook DG (2004). Passive smoking and risk of coronary heart disease and stroke: prospective study with cotinine measurement. *BMJ.* Jul 24;329(7459):200-5.

Comment 14:

- e. The Cal/EPA report cites at least ten studies that have evaluated the association of breast cancer with active or passive smoking in relation to specific genetic polymorphisms (Ambrosone 1996, Millikan 1998, Morabia 2000, Chang-Claude 2002, Zheng 1999, Gammon 1999, Conway 2002, Brunet 1998, Ishibe 1998, Zheng 2002). All of these studies have limited statistical power to assess gene-environment interactions, and report conflicting findings (Figures 4a-4d). For example, Ambrosone 1996 found increased risk of post-menopausal breast cancer associated with active smoking only among women with slow acetylator NAT2 genotype. This conflicts with the findings of Morabia 1998, which showed increased risk in both slow and rapid acetylators and with the results of Millikan 1998, who found no association for either genotype. Even more limited are studies regarding polymorphisms in NAT1 (Zheng 1999), p53 (Gammon 1999), or BRCA1 and BRCA2 (Brunet 1998). While it is legitimate to hypothesize that genetic susceptibility may modify the relationship between tobacco smoke and breast cancer (pgs 7-132 & 7-133), the hypothesis is not currently supported by studies of this issue. The inclusion of Figure 7.4.3 (page 7-138) suggests that the results currently available on genetic susceptibility provide reasonable support for a causal relationship between ETS and breast cancer. Since this is not the case, we suggest that Figure 7.4.3 be dropped unless it is used to illustrate the inconclusiveness of currently available data.

Response:

Figure 7.4.3 was inserted to illustrate another point made in the text. Unfortunately, that point was missed when one only considered the figure itself and thus was confusing to several

commenters. We appreciate Dr. Thun's suggestion and figure 7.4.3 has been removed. While we agree that any genetic susceptibility modifying the relationship between tobacco smoke and breast cancer has yet to be firmly established, the majority of studies now find either statistically non-significant or significant interactions between human genetic characteristics, smoking, and breast cancer incidence. The level of statistical significance is a function of the size of these studies which have been limited by financial and other considerations. Additionally, accounting for the full spectrum of interactions necessary to fully explore possible risk is difficult as there may be interactions between age at exposure, age at first pregnancy, intensity and duration of exposure, genetic phenotype, etc. A meta-analysis of the various studies is not feasible since there are few studies which have measured outcomes for the same variables. Below is a chart of recent studies exploring genetic polymorphisms and susceptibility to breast cancer among active smokers which we have added to the active smoking section of the document. As noted in the chart, there are some studies which indicate strong effects of metabolic enzyme profiles, although others may not. Looking at a single enzyme does not give the complete picture because there are many different carcinogens in tobacco smoke metabolized by several different enzymes (both Phase I and Phase II). Thus the resulting net effect for a given individual depends on the entirety of the metabolic enzyme profile as far as dose of ultimate carcinogen is concerned. In addition, Couch et al. (2001) found that those smokers with high familial rates of breast and ovarian cancer have high elevated risk of breast cancer compared to nonsmokers. The point we are making is that genetics plays a role in chemical carcinogenesis and there appears to be susceptible subpopulations for carcinogenicity of tobacco smoke.

Gene Polymorphisms and Genetic Susceptibility to Breast Cancer Among Active Smokers

<i>Study</i>	<i>Polymorphism</i>	<i>Target group</i>	<i>Comparison group</i>	<i>OR (95% CI)</i>
<i>Millikan et al., 1998</i>	<i>NAT2¹ fast</i>	<i>Quit smoke ≤ 3 yr</i>	<i>Never smoker with or without ETS exposure</i>	
		<i>Postmenopausal</i>		7.4 (1.6; 32.6)
		<i>Premenopausal</i>	“	1.5 (0.6; 4.0)
	<i>NAT2 slow</i>	<i>Postmenopausal</i>	“	2.8 (0.4; 8.0)
		<i>Premenopausal</i>	“	1.9 (0.5; 7.9)
		<i>Current smokers</i>		
	<i>NAT2¹ fast</i>	<i>Postmenopausal</i>	“	1.4 (0.7; 2.8)
		<i>Premenopausal</i>	“	1.1 (0.5; 2.3)
		<i>Postmenopausal</i>	“	1.1 (0.6; 2.2)
	<i>NAT2 slow</i>	<i>Premenopausal</i>	“	0.8 (0.4; 1.6)
<i>Morabia et al., 2000</i>	<i>NAT2 fast</i>	<i>Postmenopausal</i>	<i>Never-smoker, no ETS</i>	8.2 (1.4; 46.0)
	<i>NAT2 slow</i>	“	<i>ETS only</i>	2.5 (1.0; 6.2)
	<i>Fast & slow</i>	<i>Premenopausal</i>	<i>Never-smoker, no ETS</i>	2.9 (1.1; 7.5)
<i>Delfino et al., 2000</i>	<i>NAT2</i>	<i>Postmenopausal</i>	<i>Low risk controls</i>	1.29 (0.74 ; 2.27)
		<i>Premenopausal</i>		1.15 (0.49 ; 2.79)
		<i>All ages</i>		1.25 (0.27; 5.82)
<i>Krajinovic et al., 2001</i>	<i>NAT2 fast</i>	<i>BC² smokers (pre- & post)</i>	<i>BC nonsmokers</i>	2.6 (1.1; 6.3)
<i>Chang-Claude et al., 2002</i>	<i>NAT2 fast</i>	<i>Pre- and post-menopausal</i>	<i>Never-smoker, no ETS</i>	1.22 (0.59; 2.54)
	<i>NAT2 slow</i>		“	1.67 (0.67; 2.89)
<i>Zheng et al., 2002</i>	<i>GSTT1³ null</i>	<i>Smoke start <18 Postmenopausal</i>	<i>Never-smokers</i>	2.9 (1.0; 8.8)

	<i>GSTT1</i> positive			1.1 (0.6; 1.9)
	<i>GSTT1</i> null	Pre- and post-	Never-smokers	1.7 (0.8; 3.7)
	<i>GSTT1</i> positive	Menopausal		1.0 (0.7; 1.6)
		Current smokers		
	<i>GSTT1</i> ³ null	Postmenopausal	Never-smokers	2.3 (0.6; 8.9)
	<i>GSTT1</i> positive			1.1 (0.6; 2.1)
	<i>GSTT1</i> null	Pre- and post-	Never-smokers	1.1 (0.4; 2.7)
	<i>GSTT1</i> positive	Menopausal		1.1 (0.6; 1.9)
Saintot et al., 2003	Val CYP1B1 ⁴	Pre- and post-	Lew/Leu nonexposed	2.32 (1.00; 5.38)
	His SULT1A1 ⁵	menopausal	Arg/Arg nonexposed	2.55 (1.21; 5.36)
	Met COMT ⁶		Val/Val nonexposed	1.42 (0.65; 3.13)
Couch et al., 2001	High familial	1 st degree relative	Never-smokers	1.8 (1.2; 2.7)
	BC risk	2 nd degree	“	1.1 (0.8; 1.5)
		Married in	“	1.2 (0.9; 1.6)
	Highest risk (5+ family members affected) ⁷	Sisters and daughters		
		SMR	“	5.8 (1.4-23.9)
				2.3 (0.9-6.0)

¹NAT2 = N-acetyltransferase; ²BC = breast cancer; ³GSTT1 = Glutathione S transferase T1 ⁴CYP1B1 = Cytochrome P-450 1B1; ⁵SULT1A1 = Phenol-sulphotransferase 1A1; ⁶Catechol-O-methyltransferase; ⁷Highest risk families were defined two ways: those with five or more members with either ovarian of breast cancer or those with two or more observed cancers than expected. From the latter definition was derived the number based on the SMR.

Comment 15:

- f. Studies of the timing of tobacco smoke exposure in relation to breast cancer risk are similarly inconsistent (Figure 5). Two studies (Morabia 1996 & Lash 1999) report an equivalent increase in risk associated with active smoking whether smoking began before or after the first pregnancy; Band 2002 reports an association with premenopausal breast cancer only when active smoking occurs before the first pregnancy; Kropp 2002 and Egan 2002 report no significant difference related to the timing of exposure. Reynolds

2004 reports some increase in the risk of postmenopausal breast cancer in women who smoked at least five years before first pregnancy.

Response:

While there is not total uniformity described by your figure 5, the figure does reflect an increase in risk measured in at least some portion of the metrics of five of six of the studies presented in the “exposure prior to first pregnancy” portion. Some inconsistencies in what has been observed with regards to timing and risk may be the result of random variation related to relatively small numbers in the critical exposure groups. It should be noted that the OR plotted for Egan is not significant but that they report, for smokers who started before age 16, an OR of 1.31 (CI 1.07-1.61). Johnson (not included in your figure 5) reports for premenopausal breast cancer and starting smoking before age 15 an OR of 2.1 (CI 1.0-4.3). A number of studies have demonstrated elevated risk resulting from exposure during a period of breast development at least for some metrics. An exact understanding of the dynamics of the critical exposures has not been established and existing measures may be sub-optimal for consistently teasing out the risk, because it appears to be more complex than a straight dose-response relationship.

Comment 16:

- g. The data in figures 2-4 are equally inconsistent with regard to risk of pre versus postmenopausal breast cancer in studies of active smoking or ETS exposure. The currently available data do not convincingly demonstrate a stronger association of ETS with any particular type of breast cancer, nor do they establish that past studies underestimated the association by studying the wrong endpoint.

Response:

Please refer to the response to comment 8.

Specific comments:

Comment 17:

Page 7-79 through 7-81: It is important not to confuse studies of nasopharyngeal cancer with those pertaining to nasal sinus cancer. Both are extremely rare in the United States, but nasopharyngeal cancer is not rare in certain Asian and native-Alaskan populations. The only studies cited that pertain to nasal sinus cancers were those reviewed in the 1997 Cal/EPA report. All of the newer studies pertain to nasopharyngeal cancer.

Response:

The comment is correct and the text will be changed to reflect the different cancer sites. There are no new studies specifically addressing nasal sinus cancer to alter the conclusion in the 1997 document of an association with ETS exposure. It is of interest to note that in a comparison of the risk factors for sinonasal and nasopharyngeal cancers, Zhu et al. (2002) report that smoking was a risk factor for squamous cell tumors at both sites. It is anticipated that ETS also would have similar effects in both sites.

As mentioned in our response to comments by M. LeVois, the results of the Yuan et al. (2000) study suggest a gender difference in cancer susceptibility in which females are more at risk for nasopharyngeal cancer after ETS exposure. For both males and females there is evidence of a dose-response for childhood exposure to both maternal and paternal smoking, although in males the confidence intervals include no effect. The study by Armstrong et al. (2000) did not find an association between nasopharyngeal cancer and ETS exposure in adulthood, but there was a significant association between childhood exposure to parental smoking and subsequent nasopharyngeal cancer (OR 1.54; $p = 0.040$). This is consistent with the results of Yuan et al. for females and may indicate a developmental window of susceptibility. More recent studies suggest an association between childhood ETS exposure and subsequent development of nasopharyngeal cancer but leave the role of ETS exposure in adulthood undecided.

Comment 18:

IARC reviewed the studies of active and passive smoking in relation to cancers of the nasopharynx, nasal cavity, and paranasal sinuses. IARC concluded that active smoking was causally related to cancers of the nasal cavity and paranasal sinuses, but that the evidence regarding ETS exposure was "conflicting and sparse". It was considered implausible that the association seen with ETS in these studies was stronger than that seen with active smoking.

Response:

With respect to active smoking and nasopharyngeal cancer, IARC reported:

“An increased risk for nasopharyngeal cancer among cigarette smokers was reported in one cohort study and nine case–control studies. Increased relative risks were reported in both high- and low-risk geographical regions for nasopharyngeal cancer. A dose–response relationship was detected with either duration or amount of smoking. A

reduction in risk after quitting was also detected. The potential confounding effect of infection with Epstein–Barr virus was not controlled for in these studies; however, such an effect was not considered to be plausible. No important role was shown for other potential confounders.”

In reporting that an association between ETS and nasopharyngeal cancer is unlikely to be stronger than that seen with active smoking, IARC has not ruled out an ETS effect. A plausible explanation for the apparently disparate effects of ETS versus active smoking may lie in the window of exposure mentioned above. In those studies, childhood exposures to ETS were associated with a greater risk of nasopharyngeal cancer while adult exposures were not. In addition, as implied in IARC’s statement, nasopharyngeal cancer is strongly associated with infection by Epstein-Barr virus (EBV). In vitro, B lymphocytes infected with lytic EBV were found to be susceptible to chemical induction by extracts of smokeless tobacco in terms of decreased cell population growth, and increased cell death and apoptosis (Jenson et al., 1999). Although it is not clear whether there is an interaction between tobacco smoke and EBV in the induction of at least some nasopharyngeal or sinus cancers, it is certainly plausible.

Comment 19:

- 1) Page 7-92, Active Smoking, line 6: The Wartenberg et al. 2000 study considered only second-hand smoke and should not be listed here. The correct reference is Cable et al., 1994 (S), who studied active smoking in relation to fatal breast cancer in the ACS cohort. The study by Terry et al. 2002 should be cited here rather than on page 7-122 (2nd last line) because it concerns active smoking.

Response:

Thank you for pointing out these inconsistencies. The revised document will show these corrections.

Comment 20:

- 2) Page 7-134, 2nd full pp, 1st sentence: While it is true that there is concordance between animal and human susceptibility to carcinogenesis from a particular exposure, there is much less concordance with the affected site.

Response:

OEHHA agrees that this is generally the case, and in fact goes on to argue later in the same paragraph that this may result in an underestimate of the number of potential human mammary carcinogens in tobacco smoke, since a case can be made (based on background rates of incidence) that human mammary tissue is a relatively sensitive site compared to some rodent models where other sites (e.g. liver, lung) have very high background rates and/or apparent sensitivity to chemical carcinogens.

Comment 21:

- 3) Page 7-134, last pp: The report should acknowledge that animal models of mammary cancer are less predictive of human breast cancer than are animal models of certain other cancer sites.

Response:

OEHHA does not agree with this assertion in the general form stated. Since the comment does not specify which other sites are to be referred to for comparison, a detailed response is difficult. There is also a concern that this comment may represent a prejudgment of the issue, since apart from tobacco- and alcohol-related effects most of the human evidence on induction of breast cancer by extrinsic chemical agents is based on prevalence or “ecological” studies that are notoriously hard to evaluate. Most of the clear-cut comparisons between animal and human cancer responses depend for the human evidence on occupational cohorts and case groups, in which women are notoriously under-represented.

Comment 22:

- 4) Page 7-136, 1st pp, 1st sentence: While the sentence is technically true, three of the studies cited (Santella 2000, Rundle 2000, and Li 2002) mention finding no association between smoking status and the formation of DNA adducts or oncogene formation in breast tissue.

Response:

As noted in the comment, OEHHA avoided claiming that any such association was either expected or found; the point is that mammary tissue is susceptible to the same sort of genetic alterations, in response to polycyclic aromatic hydrocarbon exposures, that are known

precursors of tumor appearance in other tissues. Given the difficulties in establishing the degree of tobacco smoke exposure from measures of smoking status detailed in the document; it is unremarkable that some of these studies failed to demonstrate this latter association. In addition to the sources cited in the draft report, the following should also be considered:

Firozi et al (2002) and a previous paper by Li et al. (1996) measured aromatic DNA adducts in breast tissue from cancer patients and controls. They found higher levels of DNA adducts in smokers than in non-smokers, and in non-cancerous tissue adjacent to a tumor than in tissue from the actual tumor. Dependence of adduct levels on polymorphisms of Cyp1A1 and NAT2 (genes specifying enzymes important in PAH metabolism) was also noted in smokers but not in non-smokers. Gene-gene interaction was also noted in smokers with certain CYP1A1 and GSTM1 null polymorphisms combined having much higher levels of DNA adducts than either individually. Their findings suggest that polymorphisms of CYP1A1, GSTM1, and NAT2 significantly affect either the frequency or the level of DNA adducts in normal breast tissues of women with breast cancer, especially in smokers.

Firozi PF, Bondy ML, Sahin AA, Chang P, Lukmanji F, Singletary ES, Hassan MM, Li D (2002). Aromatic DNA adducts and polymorphisms of CYP1A1, NAT2, and GSTM1 in breast cancer. *Carcinogenesis* 23(2):301-6.

Li D, Wang M, Dhingra K, Hittelman WN. (1996). Aromatic DNA adducts in adjacent tissues of breast cancer patients, clues to breast cancer etiology. *Cancer Res.*, 56:287-293.

Similarly, Faraglia et al. (2003) examined both normal and cancerous breast tissues from breast cancer patients for adducts related to 4-aminobiphenyl, a known carcinogen and tobacco smoke constituent. For normal tissues of current smokers, former smokers and non-smokers, a significant linear trend ($P = 0.04$) was observed between DNA adducts and smoking status. Consideration of both active and passive status (never either, ever passive only, ever active only, ever both) also showed a linear trend in the level of DNA adducts in normal tissue with smoking status ($P = 0.03$). An increase in adduct levels with passive smoking status alone (never, former, current) was seen but the trend was not statistically significant: a significant limitation of the data set examined in this study was the small number of cases reporting neither active nor passive smoking.

Faraglia B, Chen SY, Gammon MD, Zhang Y, Teitelbaum SL, Neugut AI, Ahsan H, Garbowski GC, Hibshoosh H, Lin D, Kadlubar FF, Santella RM (2003). Evaluation of 4-aminobiphenyl-

DNA adducts in human breast cancer: the influence of tobacco smoke.
Carcinogenesis **24**(4):719-25.

The revised report will include these two important references.

Comment 23:

- 5) Page 7-136, 1st pp, last sentence: Whyatt et al. 1998a measured DNA adducts in placental tissue; Anderson et al. 2001 measured urinary excretion of nicotine metabolites. These studies do not directly involve breast tissue.

Response:

OEHHA did not intend to imply that they did so, but used these examples to demonstrate that humans exposed to ETS are subject to internal (metabolic) exposures characteristic of polycyclic aromatic hydrocarbons and similar compounds that have been identified as components of ETS. Clarification of this will be added to the document along with the information on DNA-adducts presented in above response to comment 5.

Comment 24:

- 6) Page 7-136, 2" pp: None of the studies cited above document DNA adducts or mutations in breast tissue due to ETS.

Response:

See above responses to comments 5 and 6.

Comment 25:

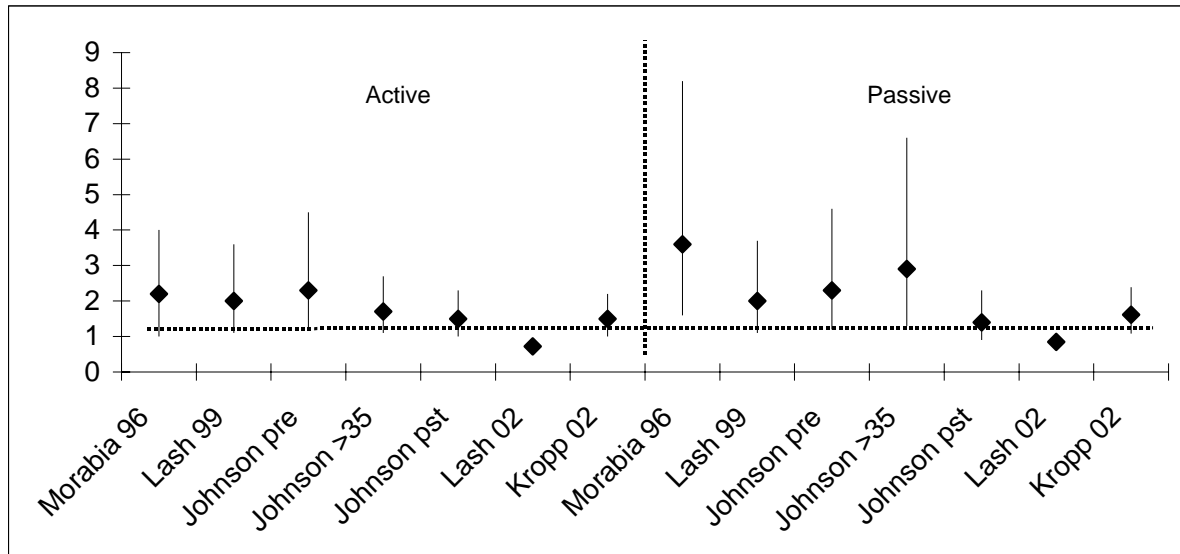
- 7) Page 7-137, Figure 7.4.2: The horizontal dotted line should represent a RR of 1.0 on the Y axis, not be below it. If this line is repositioned the results by Lash 2002 will be below the line. The selection of studies included in this graph is puzzling. The subgroup findings from Johnson for women > 35 years should not be included, whereas the results from Morabia 1996, ChangClaude 2002, Egan 2002, and Reynolds 2004 should be added.

Response:

The dotted line location is an artifact of the word processing program and we will correct that. Morabia has been added per your suggestion. Chang Claude 2002 is not considered separately

since it utilizes the participants of the same study as Kropp 02 which is included. Reynolds and Egan are not included since they were not considered to be examples of studies that had complete measures of lifetime exposure to ETS in various settings.

Figure 7.4.2. Recent studies of breast cancer risk utilizing an unexposed referent group



Comment 26:

- 8) Page 7-138, top pp: The issue of the "consistency" of results from the case-control studies only becomes important if one has satisfied considerations of validity.
- 9) Page 7-13, top pp & Figure 7.4.3: See general comment 3c above.

Response:

The issues regarding validity of the case-control studies are addressed in several of the other responses to Dr. Thun's comments including comments 11, 12, and 13.

Comment 27:

- 10) Page 7-144, Figure 7.4.4: The scale on the Y-axis should consistently be either arithmetic or log transformed but not both. Use of the log-transformed scale may obscure the degree of variability across studies and the implausibly large RR estimates in some studies. Hirayama 1984 or Sandler 1985 should presumably not be included in the Figure, since their published analyses were incomplete and did not control for the established risk factors for breast cancer.

Response:

We have in general used a log transformed scale for the figures. The log scale is preferable for RRs because it more accurately reflects the magnitude of the effect. E.g., on the log scale, the physical distance between 0.5 and 1 is the same as between 1.0 and 2.0 and between 2.0 and 4.0 (all reflect a 2x difference in relative risk). In some instances it was felt to be visually more appropriate to present the data in an arithmetic form. When clarity demanded consideration of alternative formatting we allowed for what we felt was the most clear presentation. Each study presents strengths and weaknesses that need evaluation.

In our evaluation Hirayama and Sandler were of adequate quality to consider in the more complete analysis of the data. You can see that they are given an open diamond which while signifying having missed likely sources of exposure allows you to see in the summary statistic “with important ETS sources included” that removing these studies in fact results in a stronger association with breast cancer. The analysis was robust to inclusion or exclusion of various studies.

Comment 28:

- 11) Page 7-146, Figure 7.4.5: Several studies included in this figure do not control for important covariates such as age at first birth and/or alcohol consumption (Hirayama 1984, Sandler 1985, Smith 1994, Millikan 1998, Delfino 2000).

Response:

All of the studies mentioned above in #11 except Smith are considered in our analysis as lower quality studies and are designated with an open diamond. While it is true that the primary consideration for open diamond was based on the completeness of the exposure history, you can conveniently observe the effect of dropping these studies on the summary statistic by looking at the RR-important ETS sources collected. Smith we believe correctly belongs in the grouping of more complete studies. Their data on passive smokers included adjustments for age, age at menarche, age at first full term pregnancy, breastfeeding, total oral contraceptive use, family history, and alcohol consumption at age 18 years. This study only considered subjects under 36 years of age and therefore consumption at 18 (the time of highest quantity of consumption) was considered a reasonable measure. Though there was some difference in alcohol consumption at

ages 18, 25, and at diagnosis, various analyses were performed for each age and none found statistically significant change in the impact on breast cancer.

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Figure 1: Studies of Breast Cancer and active smoking

Figure 2: Breast cancer & ever smoking by subgroup

Figure 3. RR for Breast Cancer Among Current Active Smokers When Referent Group Includes (+) or Excludes (-) ETS Exposed Women

Figure 4a. NAT2 Susceptibility to Develop Breast Cancer from Current Active Smoking

Figure 4b. NAT2 Susceptibility to Breast Cancer for Women ever exposed to ETS

Figure 4c: Genetic Subgroup Susceptibility to Breast Cancer from Current Active Smoking

Figure 5. Timing of smoking and breast cancer risk